The fetal origins of sexual dimorphism in the mammalian germline

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Mammalian oocytes and spermatozoa derive from a fetal cell type shared by the sexes: the primordial germ cell (PGC). PGCs migrate to the developing somatic gonad, where they ultimately give rise to either oocytes or spermatozoa. These opposing sexual fates are determined not by the PGCs' own sex chromosome constitution (XX or XY), but by the sexual identity of the fetal gonad to which they migrate. We asked whether PGCs undergo a developmental transition that enables them to respond to feminizing or masculinizing cues from the fetal ovary or testis. We conducted *in vivo* genetic studies of DAZL, an RNA-binding protein expressed in both ovarian and testicular germ cells. We found that germ cells in C57BL/6 *Dazl*-deficient fetuses – whether XX or XY – complete their migration to the gonad but acquire no demonstrable features of either male or female differentiation. Instead, they retain a sexually undifferentiated state similar to that of migrating PGCs. Thus, germ cells in C57BL/6 *Dazl*-deficient fetuses do not respond to sexual cues provided by the ovary or testis, while the earlier processes of germ cell specification and migration are unaffected. We propose that PGCs of both XX and XY fetuses undergo an active developmental transition, which we term licensing, that enables the resultant gametogenesis-competent cells to respond to feminizing or masculinizing cues produced by the fetal ovary or testis, and hence to embark on oogenesis or spermatogenesis. In C57BL/6 mice, *Dazl* is required for licensing. Licensing serves as a gateway from the embryonic processes shared between the sexes – germ cell specification and migration – to the sex-specific pathways of oogenesis and spermatogenesis.

Related prior work:

Menke DB, Koubova J, Page DC (2003) Sexual differentiation of germ cells in XX mouse gonads occurs in an anterior-to-posterior wave. *Dev Biol* 262:303-12.

Baltus AE, Menke DB, Hu Y, Goodheart ML, Carpenter AE, de Rooij DG, Page DC (2006) In germ cells of mouse embryonic ovaries, the decision to enter meiosis precedes premeiotic DNA replication. *Nat Genet* 38:1430-4.

Koubova J, Menke DB, Zhou Q, Capel B, Griswold MD, Page DC (2006) Retinoic acid regulates sex-specific timing of meiotic initiation in mice. *Proc Natl Acad Sci* 103:2474-9.

Anderson EL, Baltus AE, Roepers-Gajadien HL, Hassold TJ, de Rooij DG, van Pelt AMM, Page DC (2008) *Stra8* and its inducer, retinoic acid, regulate meiotic initiation in both spermatogenesis and oogenesis in mice. *Proc Natl Acad Sci* 105:14876-80.

Lin Y, Gill ME, Koubova J, Page DC (2008) Germ cell–intrinsic and –extrinsic factors govern meiotic initiation in mouse embryos. *Science* 322:1685-7.